Complete Summary

GUIDELINE TITLE

The role of chemotherapy with radiotherapy in the management of patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer.

BIBLIOGRAPHIC SOURCE(S)

Head and Neck Cancer Disease Site Group. Thephamongkhol K, Browman G, Hodson I, Oliver T, Zuraw L. The role of chemotherapy with radiotherapy in the management of patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Mar [online update]. 20 p. (Practice guideline report; no. 5-7). [25 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Otolaryngology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate if the addition of chemotherapy to radiotherapy improves the survival of adult patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer and, if it does, to evaluate the best timing and regimen of chemotherapy

TARGET POPULATION

Adult patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer (stage III or IV) who are being considered for radiotherapy as the definitive modality for curative intent and who can tolerate chemotherapy, in the judgment of the treating oncologist

INTERVENTIONS AND PRACTICES CONSIDERED

1. Radiation alone
2. Cisplatin-based chemotherapy plus radiotherapy

MAJOR OUTCOMES CONSIDERED

- Complete response
- Local failure rates
- Overall survival
- Disease-free survival
- Median survival
- Point in time survival
- Chemotherapy toxicity

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Original 2003 Guideline

The literature was searched using MEDLINE (OVID; 1966 through March 2003), EMBASE (OVID;1980 through March 2003), the Cochrane Library (OVID; Issue 4, 2002), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology

(1997–2002), the American Society for Therapeutic Radiology and Oncology (1992–2002), the Asian Clinical Oncology Society (2001), the International Congress of Radiation Oncology (1997 and 2001), the European Society of Therapeutic Radiology and Oncology (1992, 1994, 1996, 1998, 2000, 2002), and the European Society for Medical Oncology (2000, 2002). Article bibliographies and personal files were also searched to March 2003 for evidence relevant to this practice guideline report.

The literature search combined nasopharyngeal disease specific terms (nasopharyngeal neoplasms/ or nasopharyn:.mp. or nasopharyngeal.tw.) with treatment specific terms (drug therapy/ or chemotherapy/ or chemotherapy.tw. or radiochemotherapy.mp. or chemoradiotherapy.mp.) and search specific terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, and clinical trials.

March 2004 Update

The original literature search has been updated using MEDLINE (March 2003 through March 2004), EMBASE (March 2003 through March 2004), the Cochrane Library (Issue 1, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2003) and the American Society for Therapeutic Radiology and Oncology (2003). Article bibliographies and personal files were also searched to March 2003 for evidence relevant to this practice guideline report.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published reports or published abstracts of randomized controlled trials that reported the following:

- Data on the treatment population of interest; i.e., newly diagnosed patients with locally advanced squamous cell or undifferentiated nasopharyngeal cancer
- Data on patients receiving any combination of chemotherapy plus radiation in the neoadjuvant, concurrent, or adjuvant setting (intervention) versus radiotherapy alone (control)
- Results for the primary outcomes of interest: disease-free survival and/or overall survival, or for the secondary outcomes of interest: local control, response, toxicity, and/or quality of life

Practice guidelines, meta-analyses, or systematic reviews explicitly based on randomized trials related to the guideline question were also eligible for inclusion in the systematic review of the evidence.

Exclusion Criteria

Articles were excluded from the systematic review of the evidence if they were trials that did not report separate results for patients with nasopharyngeal cancer.

NUMBER OF SOURCE DOCUMENTS

Original 2003 Guideline

Seventeen randomized trials with 20 comparisons were eligible for inclusion and review.

March 2004 Update

One meta-analysis was identified.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Original 2003 Guideline

The primary outcomes of interest are overall and disease-free survival. To estimate the effect of chemotherapy added to radiotherapy on overall and disease-free survival, the results of the randomized trials were pooled where appropriate using the meta-analytic software program RevMan 4.1 (Metaview © Update Software). Individual patient data were not available for the analysis. Where two-year survival data were not reported, data were estimated from published survival curves. In the case of missing data, authors were contacted for further information.

The proportion of patients who relapsed and those who died at a specified time point were pooled across studies. The common time point of two years was selected, as most of the trials reported sufficient follow-up (greater than 50%) at two years, and two-year survival is a clinically reliable point for relapse and/or recurrence. Abstract data were eligible for inclusion in the pooled analysis. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI) for an event (i.e., mortality or relapse) such that estimates less than 1.0 favour chemoradiotherapy and estimates greater than 1.0 favour radiotherapy alone. Results are also expressed as the number needed to treat (NNT). Data were analyzed using the random effects model. Data were to be pooled across trials by timing of chemotherapy. In the event of statistical heterogeneity, sensitivity analyses were to be performed.

Two trials compared multiple treatment arms. In pooling the data, the treatment arms were categorized as separate trials comparing each treatment arm with the same control arm.

March 2004 Update

The methods to combine the results between hazard ratio [HR] and OR were discussed by members of the Head and Neck Disease Site Group (DSG). Given the presence of crossing survival curves in seven trials, indicating that the assumption of a constant hazard ratio has been violated, the proportion of patients who relapsed and those who died at a specified time point were pooled across studies. To avoid error associated with loss to follow-up or patient censoring, the common time point of two years was selected, as most of the trials reported sufficient follow-up (greater than 50%) at two years, and two-year survival is a clinically reliable point for relapse and/or recurrence. Results are also expressed as the number needed to treat with the 95% confidence interval using the inverse of the risk difference.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Based on the evidence described in the original guideline document, the Head & Neck Cancer Disease Site Group (DSG) drafted the recommendations. Please note that the trial data by Lin et al were not available at the time of practitioner review. The draft recommendations were largely driven by the only randomized trial to detect an improvement in overall survival. However, there were significant concerns with the existing body of evidence, and in the absence of further data, current practice and the best available evidence was used as the basis of the draft recommendations. After practitioner feedback was completed, the recommendations were strengthened significantly to reflect the introduction of the new positive evidence reported by Lin et al. The trial reported by Lin et al confirmed that cisplatin-based chemotherapy was more effective than radiotherapy alone. As a result of this new data, there are considerable differences in the draft and final recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 52 practitioners in Ontario (12 medical oncologists, 24 radiation oncologists, and 16 surgeons). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Head and Neck Disease Site Group (DSG).

The practice guideline report was circulated to 14 members of the Practice Guidelines Coordinating Committee (PCCC) for review and approval. Seven of the 14 members returned ballots. Six PCCC members approved the practice guideline report as written. One member approved the report with modifications (detailed in the original guideline document) required.

The practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process and the introduction of new data from the trial by Lin et al.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- It is recommended that cisplatin-based concurrent radiochemotherapy be routinely offered to patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer (stage III or IV).
- Of the two trials with cisplatin-based concurrent chemotherapy that showed a survival difference, one included adjuvant chemotherapy, while one did not. It is recommended that either regimen may be offered to this patient population.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and a meta-analysis.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Original 2003 Guideline

- Across 12 trials with 14 comparisons, there was a significant difference in disease-free survival in favour of patients who received radiochemotherapy versus those who received radiotherapy alone (odds ratio, 0.69; 95% confidence interval, 0.54 to 0.87; p = 0.002; number needed to treat, 13); however, significant heterogeneity was detected. By timing of chemotherapy, radiochemotherapy with neoadjuvant chemotherapy (odds ratio, 0.77; 95% confidence interval, 0.59 to 0.99; p = 0.04; number needed to treat, 17), concurrent chemotherapy (odds ratio, 0.62; 95% confidence interval, 0.45 to 0.86; p = 0.004; number needed to treat, 10), or concurrent and adjuvant chemotherapy (odds ratio=0.32; 95% confidence interval, 0.11 to 0.95; p = 0.04; number needed to treat, 4) was significantly superior to radiotherapy alone.
- Across 13 trials with 15 comparisons, there was no significant difference in two-year overall survival for patients randomized to radiochemotherapy versus radiotherapy alone (odds ratio=0.77; 95% confidence interval, 0.59 to 1.01; p = 0.06; number needed to treat, 25); however, significant heterogeneity was detected. By timing of chemotherapy, radiochemotherapy with concurrent chemotherapy (odds ratio = 0.42; 95% confidence interval, 0.23 to 0.76; p = 0.004; number needed to treat, 10) or concurrent and adjuvant chemotherapy (odds ratio = 0.31; 95% confidence interval, 0.17 to 0.57; p = 0.0001; number needed to treat, 6) was significantly superior to radiotherapy alone.
- Individual results from two randomized trials detected a significant overall survival benefit with cisplatin-based concurrent (odds ratio, 0.43; 95% confidence interval, 0.22 to 0.82; p = 0.0002; number needed to treat, 8) or concurrent and adjuvant radiochemotherapy (odds ratio, 0.27; 95% confidence interval, 0.14 to 0.53; p = 0.01; number needed to treat, 4) compared with radiotherapy alone.

March 2004 Update

One meta-analysis was identified in an update search of the literature. Results are consistent with results presented in this practice guideline. In addition, the number needed to treat 95% confidence intervals were added to the key evidence section.

POTENTIAL HARMS

Original 2003 Guideline

Table 3 in the original guideline document outlines chemotherapy-related toxicity. Where reported, severe grade 3/4 toxicity associated with chemotherapy ranged from 0 to 18% for anemia, 1 to 6% for febrile neutropenia, 0 to 8% for thrombocytopenia, 2 to 38% for leucopenia, 4 to 49% for nausea/vomiting, and 0 to 8% for toxic deaths. In addition, 0 to 84% of patients experienced some grade

of alopecia. With the exception of significantly greater mucositis in the radiochemotherapy arm in the trial by Chan et al, where reported, acute radiation toxicity did not differ significantly between any of the treatment groups.

March 2004 Update

Eight of the seventeen randomized trials reported rates of toxic death with radiochemotherapy versus radiotherapy alone. Toxic death rates ranged from 0 to 8% for patients in the radiochemotherapy arms versus 0 to 2.5% for patients in the radiotherapy arms. The differences in toxic death were significant in only one trial which utilized an aggressive chemotherapy regimen.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- If concurrent chemotherapy is chosen, the recommended regimen consists of cisplatin 20 mg/m^2/day and 5-fluorouracil 400 mg/m^2 as a 96-hour continuous infusion during weeks 1 and 5 of conventionally fractionated radiotherapy.
- If concurrent and adjuvant chemotherapy is chosen, the recommended regimen consists of three doses of cisplatin 100 mg/m^2 administered concurrently on days 1, 22, and 43 of conventionally fractionated radiotherapy. In the adjuvant setting, it is recommended that 80 mg/m^2 of cisplatin be combined on day 1 with 1,000 mg/m^2 fluorouracil as a four-day continuous infusion for three monthly cycles starting four weeks after completion of radiation.
- Of the recommended chemotherapy regimens, both included patients with World Health Organization types 1, 2, and 3 nasopharyngeal carcinoma; however, stratified analyses by histology were not performed.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Head and Neck Cancer Disease Site Group. Thephamongkhol K, Browman G, Hodson I, Oliver T, Zuraw L. The role of chemotherapy with radiotherapy in the management of patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Mar [online update]. 20 p. (Practice guideline report; no. 5-7). [25 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Jul 22 (revised 2004 Mar)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Head and Neck Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Head and Neck Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of chemotherapy with radiotherapy in the management of patients with newly diagnosed locally advanced squamous cell or undifferentiated nasopharyngeal cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 29, 2004. The information was verified by the guideline developer on July 19, 2004.

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